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10/676,280	09/30/2003	Timothy R. Billiar	14022-011001	7071

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EXAMINER	
FUBARA, BLESSING M	
ART UNIT	PAPER NUMBER
1618	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/676,280	BILLIAR ET AL.	
	Examiner	Art Unit	
	BLESSING M. FUBARA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40 and 55-65* is/are pending in the application.

4a) Of the above claim(s) *4-9 and 15-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 10, 11 and 55-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/29/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges receipt of IDS filed 5/29/08. The examiner also acknowledges amendment, remarks, request for extension of time and request for continued examination under 37 CFR 1.114, all filed 04/04/08. Claims 12-14 and 41-54 are cancelled. New claims 55-65 are added. Claims 1-40 and 55-65 are pending.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/04/2008 has been entered.

Response to Arguments

Previous rejections that are not reiterated herein are withdrawn.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-3, 10, 11 and 55-65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain specific concentration of CO effective to treat

hemorrhagic shock, does not reasonably provide enablement for all concentration CO effective to treat hemorrhagic shock. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is scope of enablement.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient number of the factors are discussed below for a *prima facie* case.

1) Nature of the invention

The nature of the invention is the administration of carbon monoxide to a patient in order to treat hemorrhagic shock.

2) State of the prior art

Carbon monoxide (CO) is known in the art to be toxic to humans causing exhaustion and headache at levels of as low as 70 ppm (Omaye, "Metabolic modulation of carbon monoxide toxicity," in Toxicology 180 (2002) 139-150). The instant specification at paragraph [0040] talks about using Co at levels of 10 ppm to 3000 ppm for the treatment of hemorrhagic shock.

3) The predictability or lack thereof in the art

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific guidance is required to enable the artisan to practice the full scope of the claimed invention.

In the instant case, the scope of the claimed invention spans all concentrations of CO for effectively treating hemorrhagic shock. Also while the instant disclosure at paragraph [0040] envisions the use of 10-3000 ppm CO for inhalation, the prior art describes CO to be toxic at levels of as low as 70 ppm.

4) Amount of direction and guidance present

The direction and guidance provided is limited to amounts described in paragraph [0040] and not to all possible amounts. The listing of the amounts of CO at paragraph [0040] is an invitation to experiment because (see 5 below).

5) The presence or absence of working Examples

The working examples fail to provide any amount of CO useable in the invention, and by implication then refers back to the amounts disclosed in paragraph [0040]. The working examples do not correlate with the scope of the claims.

6) Quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of ordinary skill in the art would first need to determine what concentration of CO to use that would not provide toxicity since applicants envision concentrations of 10-3000 ppm and Omaye discloses that CO levels of 70 ppm is toxic ands the claims is open ended to any amount of CO.

Therefore, in view of the Wands factors, and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of ordinary skill in the art would have to engage in undue experimentation to test and use the scope of the claimed invention encompassed in instant claims, with no assurance of success.

This rejection can be overcome by the concentrations of CO effective for claimed method.

Response to Arguments

4. Applicant's arguments filed 04/04/08 have been fully considered but they are not persuasive.

A) Applicant states that the interview summary regarding related applications and the summary provided by Examiner Eyler indicating the issues raised in applications 10/053,535, 10/367,277, 10/600,182, 10/177,930, 11/401,722, 10/413,817, 10/371,666, and 10/455,564 during the interview with applicant's representatives, Janis K. Fraser and Todd E. Garcia should have included application 10/676,280 was to bring to the examiner's attention enablement issues raised in the other related applications that may be pertinent to the application being examined. However, while that may be so, the interview summary continues to stand and it is reiterated that there is no evidence on the record that this examined application, 10/676,280 was the subject of the interview of 21 February 2007.

B) Applicant insists that because the reference, Mayr, Ryter, Dolinay and Choi were initialed off in the disclosure statement filed 23 August 2006, the examiner !must disclaim those references for the record that the scope of enablement issues raised in the interview for 10/439,632 will not be applied against the claims of 10/676,280! With all due respect, the examiner disagrees with the applicant's premise that a reference that was never applied in this examined application must be disclaimed by the examiner for the record. The examiner would like to reiterate that statement or record for any case proceeds independently and proceeds based on the facts in that case. The references applicant wants this examiner to disclaim, that is, Mayr, Ryter, Dolinay and Choi are not of record in this application 10/676,280 and making judgments and according relevance or irrelevance on those references at this time would be premature in the examination of this application since each statement or record proceeds independently based on the facts presented in that case at any stage in the examination process. That is, the particular reference cited in applicant's other pending applications regarding enablement issues was not made of record or was not cited by the examiner in this examined application and it would be premature for the examiner to disclaim or claim for the record references applied in applicant's other applications as to the relevance or irrelevance in this application. The point is that those references are not cited in this application and attaching a signed copy of the IDS does not negate the fact that this examiner did not cite those references to support the scope of enablement raised in this application at this time.

C and D) Applicant vigorously asserts it is flawed to cite Omaye to support the fact applicant's disclosure does not support the use of all concentrations of CO because in applicant's opinion the disclosure of several concentrations of CO and applicant's use of 250 ppm in the

working example is sufficient compliance with the enablement requirement and that the office has presented no evidence suggesting otherwise. The examiner disagrees. It is brought to applicant's attention that the PTO does not have a laboratory to provide the sort of evidence applicant is seeking to support the negative teaching of Omaye as it regards the use of CO. The PTO relies on the teaching of the prior art and the use of Omaye to show that CO the negative teaching is proper and represent the evidence. Applicant's previous reply was fully addressed and the response to applicant's previous reply on the issue of Omaye and Fisher is reproduced below:

"it is noted that while issues of toxicity and side effects are not within the jurisdiction of the Patent Office but that of the FDA, the outstanding issue is the scope of the enabling disclosure relative to the scope of the claims and when the full scope of what is claimed is analyzed based on what is enabled, the question is as follows as stated in the MPEP at 2164.08 [R-2] as follows in relevant sections:

"The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims."

"The specification must teach those skilled in the art how to make and use the **full scope of the claimed invention without undue experimentation**."

"As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims."

Now, claim 1 is seeking protection for all and every amount of CO to be administered to a subject having hemorrhagic shock. The specification envisions specific concentrations for treating hemorrhagic shock. The protection sought by the claim is broader than what is enabled by the disclosure. The Omaye reference is a negative teaching and raises the issue of what levels of CO is enabled. The PTO does not have laboratories.

it is brought to applicant's attention as was stated in the office action of 1/12/07, no amounts are claimed and because artisan has to determine what works and what does not work, the experimentation is undue and the claims are seeking protection that is not commensurate with the enabling disclosure."

E, F, I) Applicant states the arguments presented in the reply of 7/22/07 was not an attempt by the applicant to import limitations from the specification into the claims. While the examiner appreciates applicants statement, it is noted that and also agreed by the applicant that the response of 7/22/07 referred to limitations that were not in the claims and such a reference to limitations in the specification that are not in the claims is an attempt to place those limitations in the claims for consideration when those limitations have not been explicitly recite. The examiner begs to disagree with the applicant on this issue.

G and H) Applicant says the argument presented regarding nitrous oxide was dismissed or issues taken with that presentation because the office misinterpreted applicant's points about NO that toxic gases such as NO could be useful therapeutically. While this may be so, there is evidence out there in the prior art, such as the Omaye teaching certain levels of Co are not suitable for use and applicant's arguments relating to NO does not overcome the

rejections since the invention is not to NO and citation of NO does not support the invention to CO.

The finding of lack of commensurate **scope of enablement** is maintained.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-3, 10 and 11 are rejected under 35 U.S.C. 102(b) as being anticipate by Fujita et al. ("Paradoxical rescue from ischemic lung injury by inhaled carbon monoxide driven by depression fibrinolysis," Nature Medicine, 7, 598-604, 2001).

Fujita discloses that inhaled CO protects against ischemic lung tissue injury (see the whole document). Inhalation meets claim 3 and lung tissue injury meets claim 1. Since ischemia is not limited to one organ and can be more generalized as in e.g. hemorrhagic shock as evidence by Bar-Or et al. (US 2005/0215468) in paragraph [0004] where it describes ischemia occurs in hemorrhagic shock in a more generalized sense. Thus Fujita meets claims 1-3, 10 and 11 because treating ischemia that occurs in hemorrhagic shock inherently treats the condition of hemorrhagic shock.

7. Claims 1-3 and 10-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Pinsky et al. (US 2005/0048133 A1).

Pinsky treats tissues damaged (paragraph [0099], [0164]) by ischemic disorders (paragraph [0017]) with carbon monoxide inhalation (paragraphs [0028]-[0030], [0049], [0055], [0061], [0062]). Ischemia is shown by the prior art to be generalized conditions deriving from hemorrhagic shock as evidenced by Bar-Or et al. (US 2005/0215468) in paragraph [0004] where it describes ischemia occurs in hemorrhagic shock in a more generalized sense. Thus Pinsky meets claims 1-3, 10 and 11 because treating ischemia that occurs in hemorrhagic shock inherently treats the condition of hemorrhagic shock.

Response to Arguments

8. Applicant's arguments filed 04/04/08 have been fully considered but they are not persuasive. Applicant argues that:

a) although ischemia can occur in hemorrhagic shock, that the office cannot use that as a general license to construe the terms "ischemia" and hemorrhagic shock as one and the same the terms. The examiner disagrees with applicant's characterization. It is well known and admitted by applicant that ischemic conditions occurs in hemorrhagic shock as evidenced by applicant's admission in the argument, paragraph [0004] of Barshalom, IngentaConnect Detection of organ ischemia during hemorrhagic shock, and Pelc et al., in Radiology, 1998, pp 219-225. The Office relies on prior art teachings as evidence and the examiner is not entirely sure why the applicant is characterizing the reliance on the prior art as license to point out what is known in the art. Two other references including applicant's admission show that ischemic conditions occur in hemorrhagic conditions and is not limited to one organ.

b -1) the claims are limited to treatment of hemorrhagic shock, that Fujita does not state of suggest that the mice experienced hemorrhagic shock or any type of generalized ischemia and that the ischemia induced by surgery in the mice was localized to the area of the lung and was not due to bleeding or hemorrhage and that Bar-Or does not support the position of the office and as such, Fujita fails to teach each and every limitation of the claims. The examiner disagrees. It is true that the claims are directed to treatment of hemorrhagic shock and as admitted by applicant, ischemia occurs in hemorrhagic shock. Thus Fujita's treatment of ischemia inherently treats hemorrhagic shock. Furthermore, the invention treats hemorrhagic shock by administering CO via inhalation (instant claim 3). Fujita administers CO via inhalation also and thus inherently treats hemorrhagic shock when ischemia, which occurs in hemorrhagic shock is treated.

b-2) Pinsky similarly fails to anticipate claims 1-3, 10 and 11 because Pinsky did not mention hemorrhagic shock any where in the disclosure and applicant argues that the ischemia in Pinsky is at discrete site according to the citation below:

“"ischemic disorder" encompasses and is not limited to a peripheral vascular disorder, a venous thrombosis, a pulmonary embolus, a myocardial infarction, a transient ischemic attack, lung ischemia, unstable angina, a reversible ischemic neurological deficit, adjunct thromolytic activity, excessive clotting conditions, sickle cell anemia or a stroke disorder.” The examiner agrees with applicant that Pinsky does not use the phrase “hemorrhagic shock,” but the examiner disagrees that Pinsky does not anticipate the claims because as admitted by applicant, ischemia occurs in hemorrhagic shock and treatment of ischemia, which occurs in hemorrhagic shock inherently teaches hemorrhagic shock. Applicant has not provided any evidence to show that

the ischemia in Pinsky cannot occur in hemorrhagic shock, the section of the Pinsky reference cited by applicant show that ischemia occurs in several cites and not located to any one organ, the section of the Pinsky reference cited by applicant does not show that ischemia does not occur in hemorrhagic shock. Pinsky anticipates claims 1-3, 10 and 11.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 55 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fujita et al. ("Paradoxical rescue from ischemic lung injury by inhaled carbon monoxide driven by depression fibrinolysis," Nature Medicine, 7, 598-604, 2001) or Pinsky et al. (US 2005/0048133 A1).

12. Fujita and Pinsky have been shown above individually to anticipate claim 1. None of these references cite the amount of CO administered to treat ischemia in ppm amounts as recited

in new claim 55. Regarding claim 56, it is within the capabilities of the artisan to determine how long the CO can be administered to effect the anticipated result of treating ischemia. The prior art teaches the general conditions of administering the CO to treat ischemia. And in general, when the general conditions of a claim are disclosed in the prior art, it is not inventive to discover optimum or workable ranges by routine experimentation. Therefore, taking the general teachings of the prior art, one having ordinary skill in the art at the time the invention was made would administer amount of CO for appropriate duration that would be effective in the treatment of ischemia and inherently hemorrhagic shock.

13. Claims 1, 2 and 57-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fujita et al. ("Paradoxical rescue from ischemic lung injury by inhaled carbon monoxide driven by depression fibrinolysis," Nature Medicine, 7, 598-604, 2001) or Pinsky et al. (US 2005/0048133 A1) in view of Peitzman et al. ("Hemorrhagic shock" in Curr Probl Surg. 1995 Nov. 32 (11): 925-1002 , abstract).

14. Fujita and Pinsky have been shown above to individually anticipate claims 1 and 2. Fujita and Pinsky did not teach further transfusion of blood to treat the ischemic condition in addition to the CO. However, Peitzman teaches that transfusion of blood is effective to treat hemorrhagic shock including ischemia. Claims 59-65 recites components that are part of the blood. Therefore, taking the teachings of the prior art, one having ordinary skill in the art at the time the invention was made, would have reasonable expectation of success that combining blood transfusion with CO administration would effectively treat ischemia and/or hemorrhagic shock because each of Co and transfusion has been shown in the art to treat ischemia/hemorrhagic shock.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BLESSING M. FUBARA whose telephone number is (571)272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Blessing M. Fubara/
Examiner, Art Unit 1618